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Research Article

Ammonium acetate as a Dual Reagent-Catalyst Role in Efficient Synthesis of 2,4,6-Trisubstituted 1,3,5-triazines from Aldehydes

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Abstract

The synthesis of 2,4,6-triaryl-1,3,5-triazines using iron-catalyzed cyclization of aldehydes with NH_4I as the only nitrogen source is shown to be an easy, atom-efficient process. This method provides symmetrical 2,4,6-trisubstituted and unsymmetrical 1,3,5-triazines with yields ranging from 52% to 85% and operates without difficulty in an environment of air. The current methodology offers a simple and atom-efficient way for making 2,4,6-trisubstituted 1,3,5-triazines that uses an affordable, widely accessible ammonium salt as the only nitrogen source.

Keywords: Ammonium acetate (NH_4OAc); Aldehydes; 2,4,6-Triaryl-1,3,5-triazines; Multicomponent reaction; Cyclization.

Introduction

In the domain of green chemistry, multi-component reactions (MCRs) have established themselves as extremely potent and effective bond-forming techniques in organic combinatorial and medicinal chemistry[1-4]. Numerous significant multi-component processes are used to synthesize heterocycles. The broadest variety of chemical compounds with significant industrial and medical applications are heterocyclic compounds, which are tremendously significant organic molecules[5-7]. Due to their biological and pharmacological properties, heterocyclic 1,3,5-triazine derivatives have recently received a lot of attention. The 1,3,5-triazine derivatives are well-known chemicals that have a great deal of interest due to their uses in a variety of industries. These substances perform a variety of functions, including those of drugs, liquid crystals, transition-metal catalysts, building blocks for supramolecular chemistry, reactive dyes, organic light-emitting diodes (OLEDs), and chemical reagents for specific transformations[8-9].

Even though substituted 1,3,5-triazines have a wide range of uses, there are presently very few ways to make these substances. Nitriles, imidates, and amidine derivatives were used as nitrogen sources in the traditional techniques of preparing substituted 1,3,5-triazines, which included cyclotrimerization of nitriles[10–16]. As a result, it has significant relevance and serves as a convenient, affordable supply of nitrogen for the synthesis of 1,3,5-triazine. For the synthesis of 2,4,6-trisubstituted 1,3,5-triazines[15], Liu and colleagues recently reported theFe-catalyzed cyclization of aldehydes with NH_4I as the sole nitrogen source. There are many accounts in the literature[17–26] about the widespread usage of ammonium acetate (NH_4OAc) as a nitrogen source in chemical synthesis. In this succinct statement, we show that the cyclotrimerization of aldehydes can utilize NH_4OAc as the only nitrogen source.

Experimental

Unless otherwise noted, all reactions were carried out in Schlenk tubes. Reagents and solvents were obtained from commercial sources and used without further purification. The ^{1}H, ^{13}C and 9F spectra were recorded on a Brucker ADVANCE III spectrometer at 400 MHz, 100 MHz and 376 MHz, and chemical shifts were reported in parts per million (ppm). Column chromatography was performed using silica gel of 300-400 μm. The GC-MS results were recorded on GC-MS QP2010 equipment. The electron ionization (EI) method was used for HRMS measurement, and the mass analyzer type is TOF for EI. The HRMS (EI) was recorded on an Esquire 3000 plus instrument.

General procedure for the synthesis of symmetrical 2,4,6-trisubstitued1,3,5-triazine (Table 1, entries 1-11)

Benzaldehyde (0.5 mmol, 1.0 equivalent), NH_4OAc (0.5 mmol, 1.0 equivalent), and $CuCl_2$ (10 mol%) were dissolved in toluene in a 25 mL RB flask (2 mL). For the amount of time listed in Table 1 under an atmosphere of air, the mixture was stirred at reflux. The reaction's product was cooled to room temperature once it was finished, and then it was diluted with ethyl acetate (10 mL), washed with water (5 mL), extracted with ethyl acetate (3-5 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. To make the product available for NMR analysis, the crude product was refined using column chromatography on silica gel (petroleum ether/diethyl ether).

2,4,6-triphenyl-1,3,5-triazine (Table 1, entry 1): White solid; mp: 238.2-239.1 ^{o}C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.80-8.78 (dd, *J* = 8.0 Hz, 6H), 8.17- 7.42 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.66, 136.26, 132.49, 128.96, 128.63. HRMS (EI): calcd for $C_{21}H_{15}N_3$: 309.1266; found: 309.1272.

2,4,6-tri-*p*-tolyl-1,3,5-triazine(Table 1, entry 2): White solid; mp: 292.1-294.4 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66-8.64 (d, *J* = 8.0 Hz, 6H), 7.37-7.35 (d, *J* = 8.0 Hz, 6H), 2.48 (s, 9H). ^{13}C NMR (100 MHz, CDCl3) δ 171.37, 142.82, 133.76, 129.30, 128.90, 21.70. HRMS (EI): calcd for $C_{24}H_{21}N_3$: 351.17335; found: 351.1738.

2,4,6-tris(4-methoxyphenyl)-1,3,5-triazine (Table 1, entry 3): White solid; mp: 220.4-222.6 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71- 8.69 (d, *J* = 9.2 Hz, 6H), 7.06-7.04 (d, *J* =9.6 Hz, 6H), 3.91 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.68, 163.08, 130.68, 129.13, 113.82, 55.41. HRMS (EI): calcd for $C_{24}H_{21}N_3O_3$: 399.1583; found: 399.1576.

2,4,6-tri-*o*-tolyl-1,3,5-triazine (Table 1, entry 5): White solid; mp: 112.3-114.7 ^{o}C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.25-8.23(d, *J* = 7.6 Hz, 3H), 7.71-7.23 (m, 9H), 2.80 (d, *J* = 13.6 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.81, 138.91, 136.16, 131.79, 131.28, 130.84, 126.03, 22.26. HRMS (EI): calcd for $C_{24}H_{21}N_3$: 351.1735; found: 351.173.

2,4,6-tris(2-chlorophenyl)-1,3,5-triazine (Table 1, entry 6): Yellow solid; mp: 201.5-203.7 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12- 8.10 (m, 3H), 7.58-7.55 (m, 1H), 7.49-7.42 (m, Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.73, 135.35, 133.63, 132.66, 131.91, 131.13, 126.99. HRMS (EI): calcd for $C_{21}H_{12}N_3Cl_3$: 411.0097; found: 411.0103.

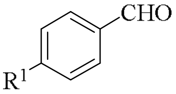
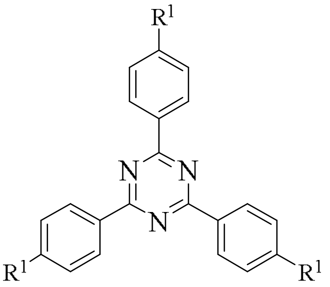
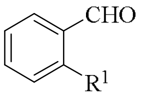
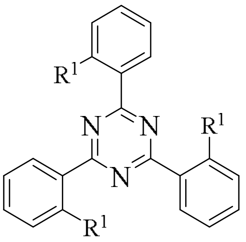
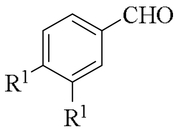
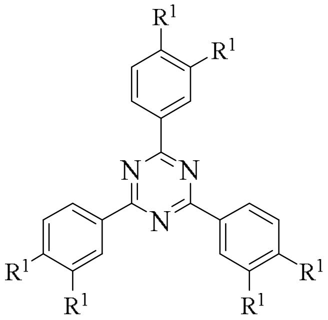
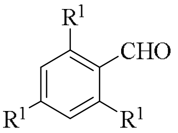
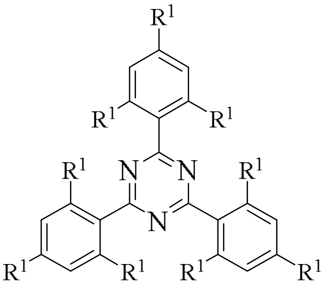
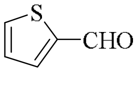
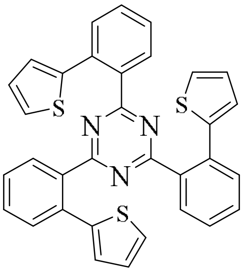
2,4,6-tris(4-fluorophenyl)-1,3,5-triazine (Table 1, entry 7): White solid; mp: 260.3-261.5 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81- 8.78 (dd, *J* = 8.7, 5.6 Hz, 6H), 7.30-7.28 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.71, 167.16, 132.21, 131.35, 131.26, 115.88, 115.67. HRMS (EI): calcd for $C_{21}H_{12}N_3F_3$: 363.0983; found: 363.0988.

2,4,6-tri(thiophen-2-yl)-1,3,5-triazine (Table 1, entry 11): White solid; mp: 183.6-185.4 ^{o}C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.28-8.27 (d, *J* = 3.6 Hz, 3H), 7.63-7.61 (d, *J* = 4.8 Hz, 3H), 7.22-7.20 (t, *J* = 4.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.69, 141.43, 132.28, 131.66, 128.38. HRMS (EI): calcd for $C_{15}H_9N_3S_3$: 326.9959.1263; found: 326.9965.

Results and Discussion

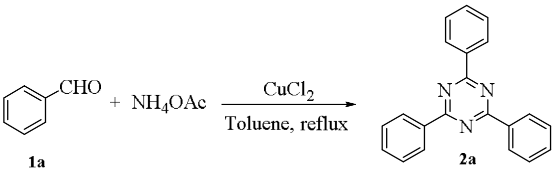
Benzaldehyde (**1a**, 1 mmol) and NH_4OAc (1 equiv) were first examined in the presence of $CuCl_2$ (10 mol%), toluene as the solvent, and reflux for 12 hours. With a yield of 68%, it was discovered that toluene is an effective solvent for the high yield synthesis of heterocyclic compounds containing nitrogen. Moderate yields of the equivalent product (**2a**) were seen when various copper salts, such as $Cu(NO_3)_2$, CuCl, CuO, CuI, and CuBr, were employed (28%, 32%, 17%, and 56%, respectively). Additionally, lowering the catalyst loading (5, 7.5% of $CuCl_2$) led to a drop in the product's isolated yield. The yield was unaffected by increasing the catalyst loading over 10 mol% either. Toluene demonstrated the best optimal outcome among the investigated solvents, including DMSO, DMF, DCM, CH_3CN, chlorobenzene, and toluene, for producing the isolated yield of **2a**. As a result, the methodology's optimal reaction conditions were set as follows: aldehyde (1 mmol), NH_4OAc (equiv.), and $CuCl_2$

Table 1. NH_4OAc-mediated synthesis of divergent 1,3,5-triazines

Entry	Aldehyde		1,3,5-triazine	time (h)	Yield (%)[a]
1		R^1= H		15	68
2		R^1= CH_3		12	72
3		R^1= OCH_3		15	75
4		R^1= F		15	65
5		R^1= CH_3		18	60
6		R^1= Cl		18	55
7		R^1= F		24	52
8		R^1= CH_3		15	78
9		R^1= CH_3		15	79
10		R^1= OCH_3		15	85
11				15	70

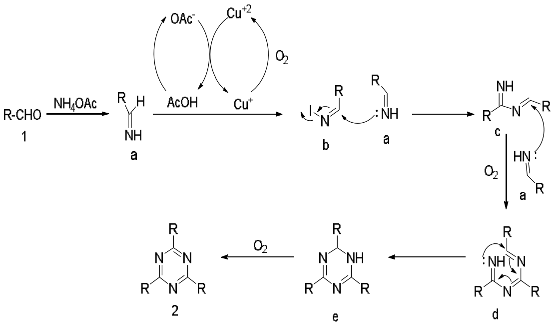
[a]Isoalted yields after column chromatography

(10 mol%) in toluene under reflux conditions (Scheme 1).



Scheme 1. NH_4OAc-mediated synthesis of 1,3,5-triazines: Control reaction

The scope of aldehyde's substrate was first assessed for the synthesis of several symmetrical 2,4,6-trisubstituted 1,3,5-triazines using the optimum reaction conditions at hand (Table 1). In this process, a variety of benzaldehydes with group substitutions that donate or take away electrons can be used, yielding the desired 2,4,6-trisubstituted 1,3,5-triazines in yields ranging from 52 to 85%. There was no discernible difference between their yields for aldehydes bearing electron-donating groups like -CH_3 and -OCH_3 and those bearing electron-withdrawing groups like –F and -Cl. They both delivered the corresponding products in sufficient yields. The required product also produced yield of 70% when heteroaryl carbaldehyde such as 2-thiphenecarboxaldehyde was utilized as substrate (Table 1, entry 11). All the synthesized products were sufficiently characterized by melting point, IR, NMR and mass spectral analyses and compared with the precedent literature data. Also investigated was the synthesis of asymmetric 2,4,6-trisubstituted 1,3,5-triazines. Low yielding complex mixtures of several possibilities have emerged.



Scheme 2: Plausible mechanism for the NH_4OAc-mediated synthesis of 2,4,6-trisubstituted 1,3,5-triazines

In Scheme 2, a viable process is shown. Aldehyde (1) and NH_4OAc first interact to create imines **a**. While this is happening, Cu^{2+} oxidizes I- to create I_2, which subsequently oxidises the imine intermediate to produce intermediate **b** of the N-iodo aldimine. An imine intermediate **c** is produced by the condensation process between imines A and intermediate **b**. The subsequent cyclization reaction between imines **a** and intermediate **c** under oxygen oxidation results in intermediate **e** in two stages. The intended product, 1,3,5-triazine, is then produced by an oxidation process that takes place on the intermediate **e** (2).

Conclusions

In conclusion, we have devised a Cu-catalyzed cyclization of aldehydes with NH_4OAc for the moderate to good yield synthesis of both symmetric and unsymmetric 2,4,6-trisubstituted 1,3,5-triazines. The substrate range for this approach is rather large. Importantly, NH_4OAc was used as the only supply of nitrogen. This procedure offers a quick and effective way to create important 1,3,5-triazines.

Conflicts of interest

None

Funding Details

Not applicable

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